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HLA-DRB1 association in Turkish psoriasis vulgaris patients

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Psoriasis vulgaris (PV) is a skin disease present in 1–3% of the Caucasoid population [1]. Although genetic, immunological and environmental factors foster PV, there is evidence that immune system activation plays a central role in keratinocyte hyperproliferation, a typical feature of psoriasis. Moreover, actively dividing T cells accumulate in psoriatic lesions, apart from the presence of a variety of other antigen-presenting, effector and inflammatory cells in psoriatic skin [2]. Peptide presentation by MHC class II molecules is important in human autoimmune diseases. Most of these autoimmune diseases are genetically linked to particular alleles of the class II molecules, and much sequence information has also accumulated on the polymorphisms in these genes. In some autoimmune diseases almost all of the patients carry particular alleles of MHC class II genes (e.g. pemphigus vulgaris). In other autoimmune diseases several different MHC class II alleles carry increased risk, presumably because different MHC class II molecules present the relevant peptide(s) to T cells [3].

Studies have shown psoriasis susceptibity loci on chromosomes as follows: 1, 2, 3, 4, 6th, 8th, 16, 17, 19 and 20. As seen with most autoimmune diseases, psoriasis is found on 6p and associated with allelic component of the major histocompatibility complex [4]. HLA antigens are analysed in different populations and PV has been associated with several HLA class I and class II specifities [5–9].

Among these class I phenotypes Cw6 and B57 have been most consistently reported. The alleles corresponding to these phenotypes are in linkage disequilibrium in normal individuals and compose the proximal class I end of an ancestral haplotype called EH57.1. The class II side of EH57.1 ancestral haplotype contains DRB1* 07 and some other DRB1 alleles [10]. Studies suggest several genetic backgrounds for PV [11]. The first choice is that more than one allele at a single locus may confer susceptibility. The second is that alleles at more than one locus within the HLA region may also confer susceptibility. The true disease locus could be linked to, but separate from, one or more known HLA genes. Although present HLA association information tends to support the last-mentioned hypothesis, it does not in fact rule out the first two. A close linkage between HLA class III and PV has been reported in an Indian population [12].

This study investigates HLA-DRB1 association with PV in a Turkish population.

Material and methods

Patients

The case group of this retrospective association study consisted of 59 unrelated late onset PV patients (33 males and 26 females aged 18–69 years, median age 36.75 ± 12.72) diagnosed and under the surveillance of Istanbul University Faculty of Medicine Dermatology Department. 89 control subjects were also included. The control subjects (47 males and 41 females aged 18–60 years, median age 30.07 ± 12.77) were drawn randomly from volunteer donors of Istanbul University Faculty of Medicine Bone Marrow and Stem Cell Bank.

HLA typing

DNA was extracted from peripheral blood by a standard method [13]. All patients and controls were typed at the Department of Medical Biology, Istanbul Medical School, which is accredited to perform clinical tissue typing by the European Federation of Immunogenetics (EFI). Typing was performed by the sequence specific oligonucleotide primer (PCR-SSOP) method using Dynal RELI SSO HLA-DR. Amplification was performed on a 9700 thermal cycle (PE Biosystems, CA). This is followed by hybridisation; 60 µl denaturation solution was added to each amplified product for 10–15 min at STP to allow for complete denaturation [14]. Dynal AutuReli48 automated machine (Dynal, UK) was used for detection. Hybridisation and citrate buffers are prepared 3h in advance, and substrate and conjugate solutions just before each assay. The PMP5 program was used to interpret the data.

A logistic regression model was used to analyse the data. Significance was taken as $p < 0.05$.

Results

The PV patients in this study had an average age of 36.75 ± 12.72; the minimum age was 12 and the maximum age 69. 55.9% of the PV patients (n: 33) were male and 44.1% (n: 26) female. There were 89 control subjects

Table 1

Logistic regression analysis of HLA-DRB1* alleles in psoriasis vulgaris patients.

HLA-DR	β	Sig.	Exp (β)	Confidence lower	Interval upper
DRB1*01	0.899	0.297	2.456	0.453	13.311
DRB1*15	0.288	0.781	1.334	0.174	10.198
DRB1*16	–0.052	0.961	0.949	0.119	7.578
DRB1*03	1.775	0.013	0.067	1.454	23.937
DRB1*04	–2.135	0.155	0.118	0.006	2.246
DRB1*11	–0.573	0.661	0.564	0.154	2.060
DRB1*13	–1.641	0.030	0.073	0.044	0.850
DRB1*14	–1.426	0.061	0.240	0.054	1.068
DRB1*07	–4.591	0.004	0.010	0.000	0.223
DRB1*08	–1.365	0.069	0.211	0.030	2.164
DRB1*09	2.082	0.926	8.019	0.000	7.58E+19
DRB1*10	–1.021	0.240	0.360	0.066	1.980
DR 52	0.366	0.625	1.442	0.333	6.247
DR 53	2.033	0.130	7.636	0.548	106.419
DR 51	–1.355	0.181	0.258	0.035	1.876
Constant	–3.527	0.445	0.029		

(47 male and 41 female) with an average age of 30.07 ± 12.77 (minimum age was 10 and maximum 60). PV patients had no history of smoking or drug use, nor of viral infection in the last 3 months, so that this group could be used for further research purposes (ie. chromatid exchange studies etc.).

The logistic regression model was used to analyse PV with DRB alleles, and gives a probability estimation of 35–36% for PV occurrence and 84.3% for controls, with an overall probability estimation of 64.9%.

Positive association of HLA-DRB1*03 with PV was observed (Table 1) (n: 12, p: 0.013, 95%, CI: 1.454–23.937) with a relative risk of 2.27 (Table 2). HLA-DRB1*07 association was also observed (n: 14, p: 0.004, 95% CI: 0.000–0.223) with a relative risk of 1.99 (Tables 1 and 2).

Two other HLA-DRB1 alleles have been found to be significantly related with HLA-DRB1 alleles (Table 1). These are DRB1*13 (n: 15, p: 0.030, 95% CI: 0.044–0.850) and DRB1*14 (n: 9, P: 0.061, 95% CI: 0.012–0.498.). The relative risk values for the alleles of HLA-DRB1* 13 and -DRB1* 14 are 1.10 and 1.60 respectively (Table 2).

Discussion

PV is a common HLA-associated skin disease. In the early 1990s suspicions were voiced regarding the presence of a disease gene in the HLA region, on the basis of HLA association studies. The precise genetic basis of HLA association in psoriasis has remained elusive, as it has for other autoimmune diseases [11]. This was due to the fact that little or no evidence was found for linkage to the HLA region. Recent use of genome scans has afforded stronger evidence of linkage to the HLA region [15]. Since HLA associations are well defined for PV and linkage disequlibrium is the most common explanation for allelic association, studies have emerged which reveal susceptibility genes for psoriasis [16]. Candidate psoriasis susceptibility genes have been identified in the HLA region as well as on other genes such as 1p, 2p, 3p, 4q, 8q, 16q, 17q, 19p, 20p. Genome scan studies have provided evidence of linkage to HLA over a rather broad range and not as robust as one might expect, given the strong HLA associations characteristic of PV.

Several HLA phenotypes, corresponding to alleles at the HLA-A, -B, -C, -DRB, -DQA1 and -DQB1 loci have been associated with PV [17]. HLA class II associations have been found in Russian PV patients where DR4 and DR7 antigens were significant [6].

Two susceptible haplotypes were demonstrated as follows in a Thai population [18]. 1) HLA-A2, -B13, -Cw6, -DR7, -DQA1* 0201 and 2) HLA-A2, -B17, -Cw6, -DR7, -DQA1* 0201. HLA-DQB1* 0303 was observed in Japanese psoriatics [19].

PV with early onset and family history is associated with HLA-DRB1* 0701/2, -DQA1* 0201, DQB1 0303. HLA-DRB1*07 provides a risk factor for PV when present with HLA-B27 antigen, and its absence increases the risk of presenting PV while with HLA-DQ3 [20], and HLA risk haplotype Cw 6, DR 7, DQA1* 0201 and HLA-Cw6 has been suggested with reference to the clinical picture of psoriasis vulgaris [21].

The risk we have shown for HLA-DRB1*07 is relatively high (1.99), and statistical significance observed with PV is in agreement with most recent reports.

It is of interest to note that HLA typing using DNA-based techniques gives more precise results [22, 23] than serological methods; the discrepancy was as high as 37% [24]. We have found increased frequency of HLA-DRB1* 14 (n: p <0.005, CI: 0.02–0.498). The association of HLA DRB1*14 is in agreement with a recent report in a Turkish population where only serological methods are used [25]. In this study, in addition to HLA DRB1*14 antigen two other antigen associations with PV were shown for the first time in a Turkish population.

The relation of HLA DRB1*14, -DRB1*13 and -DRB1*03 to progression of PV disease and susceptible haplotypes in Turkish psoriatics has yet to be defined.

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Table 2

HLA-DRB1* allele distribution in controls and psoriasis vulgaris patients.

HLA-DR	Patients n	%	Controls N	%	Probabilty (p)	Relative risk	Confidence lower	Interval upper
DRB1*01	4	6.8	6	6.7	0.993	1.00	0.271	3.730
DRB1*15	15	25.4	19	21.3	0.564	1.44	0.656	3.179
DRB1*16	6	10.2	12	13.5	0.546	0.89	0.307	2.608
DRB1*03	12	20.3	10	11.2	0.127	2.27	0.890	5.789
DRB1*04	8	13.6	23	25.8	0.072	0.47	0.197	1.160
DRB1*11	25	42.4	50	56.2	0.100	0.75	0.388	1.459
DRB1*13	15	25.4	21	23.6	0.800	1.10	0.514	2.369
DRB1*14	9	15.3	9	10.1	0.349	1.60	0.595	4.303
DRB1*07	14	23.7	5	5.6	0.001	1.99	0.850	4.691
DRB1*08	4	6.8	3	3.4	0.345	1.54	0.371	6.437
DRB1*09	0	–	1	0.7	0.312	1.01	0.989	1.034
DRB1*10	4	6.8	4	4.5	0.551	2.08	0.449	9.674
DR 52	42	71.2	68	76.4	0.477	0.73	0.342	1.542
DR 53	22	37.3	35	39.3	0.803	0.90	0.457	1.775
DR 51	21	35.6	26	29.2	0.414	1.318	0.653	2.661

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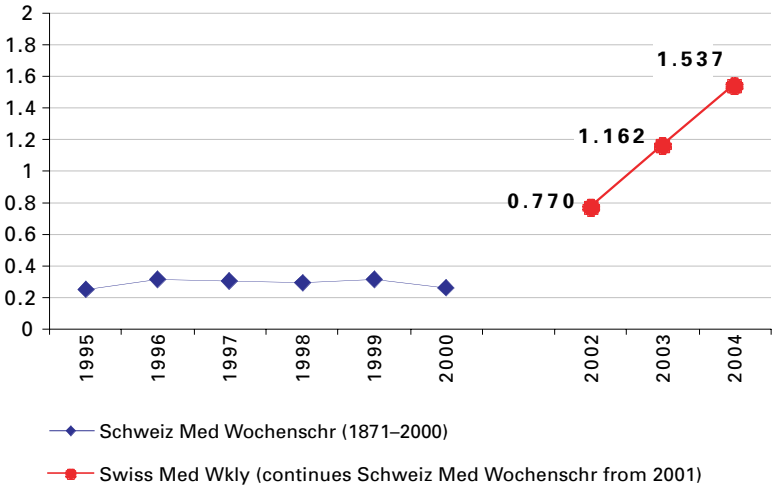

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